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MINIREVIEW

Antibiotic-Impregnated Cement and Beads for Orthopedic Infections

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HISTORICAL PERSPECTIVE

There is a long history of local antibiotic use for the treatment of orthopedic infections (13, 19, 25, 34). During World War I, Alexander Fleming observed that locally applied antiseptics failed to sterilize chronically infected wounds, but they did reduce the burden of bacteria. He also appreciated that leukocytes and tissue fluids were important factors in creating a physiological environment for promoting resolution (19). The sulfonamides were the first antimicrobial agents available for clinical use. In 1939, the instillation of sulfanilamide crystals, along with thorough debridement, hemostasis, primary closure, and immobilization, resulted in a reduced infection rate for open fractures (25). As additional systemic antimicrobial agents became available, interest in the topical treatment of wounds waned, but the management of established osteomyelitis remained problematic. In the 1960s, the method of closed wound irrigation-suction was popularized as a method which could be used to deliver high concentrations of an antibiotic after debridement. The high flow rate of hypertonic solutions by this technique eliminated hematoma accumulation and promoted the influx of leukocytes and tissue fluids. Primary closure could be accomplished to reduce cross contamination (13). An alternative method for delivering high concentrations of an antibiotic to sites of lower extremity osteomyelitis was isolation perfusion. After thorough debridement, cannulae were inserted into the appropriate artery and vein, a tourniquet was placed proximally, and oxygenated blood containing high concentrations of antibiotic was pumped through the limb (34).

The antibiotics available for the prevention and treatment of bone infections in the early 1960s were limited. Those that were used primarily included penicillin G, chloramphenicol and the tetracyclines; streptomycin and vancomycin were perceived to be toxic. The cumbersome methods of closed wound irrigation-suction and isolation perfusion were largely abandoned with the subsequent development of new systemic antibiotics which were more potent against the staphylococci and gram-negative bacilli causing orthopedic infections. Included were the antistaphylococcal and broad-spectrum penicillins, cephalosporins, lincosamides, and aminoglycosides and, more recently, the carbapenems and fluoroquinolones. Additionally, vancomycin preparations were purified, and vancomycin was no longer perceived to be highly toxic.

The local use of antibiotics to prevent and treat skeletal infections was revived in Germany with the widespread use of prosthetic joint replacement, a situation in which infections were not an anticipated consequence of trauma or sepsis but a devastating complication of elective surgery. In 1970, Buchholz and Engelbrecht (8) reported that penicillin, erythromycin, and gentamicin incorporated into the cement used to attach total hip joint prostheses diffused out into the surrounding tissues over a period of months, thereby providing prolonged concentrations of local antibiotic. On the basis of the success noted in reducing early postoperative arthroplasty infections (8), interest developed in applying antibiotic-impregnated cement as a therapy for osteomyelitis. In 1979, as an alternative to introducing large deposits of antibiotic-impregnated cement at sites of chronic osteomyelitis, Klemm (29) formed gentamicin-impregnated cement into beads and used them to temporarily fill in the dead space created after the debridement of infected bone. Among 128 patients so treated for chronic osteomyelitis, he reported a 91.4% cure rate.

Currently, antibiotic-impregnated cement is used to prevent infections primarily in arthroplasties, in which materials with adhesive properties are required; systemic perioperative prophylactic antibiotics are often given as well. Beads are used to temporarily (usually weeks to months) provide high local antibiotic concentrations and fill the dead space after debridement in patients with chronic osteomyelitis or compound fractures; again, systemic antibiotics may be given as well. After granulation tissue forms, the beads are removed and a bone graft is place (17).

Despite high initial interest in the use of antibiotic-impregnated cement and beads, controversies remain regarding their indications because of limited proof of efficacy and concerns regarding the consistency and safety of the various products available. In a 1992 survey (17), only 90 (27%) of 336 U.S. hospitals responding to the survey indicated that their physicians used antibiotic-impregnated bone cement or beads, and their use in most hospitals was only occasional. Nearly all of the 90 hospitals used the cement, but less than half used the beads.

PHYSICAL CHARACTERISTICS

Bone cement is generally a polymerized polymethylmethacrylate (PMMA), a powdered bone cement polymer which, when mixed with a liquid methylmethacrylate, polymerizes in 5 to 10 min to form an adhesive material. To incorporate antibiotics, antibiotic powder is mixed with the powdered cement polymer before the addition of the methylmethacrylate. To make beads, the mixture is molded or rolled by hand into 3- to 10-mm spheres which can be used singly or strung onto surgical suture wire (21, 22). The antibiotic used must be active against

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the targeted bacterial pathogens and must be available as a powder (pharmaceutical grade appropriate for human use rather than reagent grade) because antibiotic solutions do not mix or harden properly with the powdered bone cement polymer (31, 36). It must also be stable to the heat generated during the polymerization reaction and, subsequently, in the body's tissue.

There are various commercial preparations of antibiotic-impregnated PMMA cement. The most common types are Palacos (Merck KGaA, Darmstadt, Germany), which is used primarily on the European continent, and Simplex P (Howmedica, Rutherford, N.J.), which is used extensively in the United States and the United Kingdom (31). Commercially available gentamicin-containing Palacos PMMA cement (Palacos-Refobacin) and beads (Septopal) are produced in Germany, but no antibiotic-containing preparations are commercially available in the United States. Instead, they are prepared on site, usually in the operating room prior to use (17, 21, 22). Tobramycin is usually substituted for gentamicin, because it is available as a pharmaceutical-grade powder, whereas gentamicin is not. Mechanical tests demonstrated that the admixture of gentamicin, oxacillin, and cefazolin powders and either Palacos or Simplex P cement had no influence on their color, viscosity, set times, or compressive and diametral tension strengths (31).

In vitro analyses of antibiotic stability in cement beads or disks and their elution rates (which vary depending on conditions such as eluent solvent, pH, and the frequency of solvent exchanges) have been reported for an array of antibiotics (1–3, 21, 22, 30, 33, 46, 47). The stable incorporation and significant elution of aminoglycosides are well established (46, 47), and the primary role of this class of antibiotics in cement products is described in subsequent sections of this minireview. Both vancomycin (39) and the β-lactams (specifically, oxacillin and cefazolin) (31) can be stably incorporated into PMMA and elute well. The potential allergenicity of β-lactams has limited their widespread use in implants, while it is unclear why the use of vancomycin has not gained popularity. Clindamycin can be stably incorporated and elutes well, but it is not available as a pharmaceutical-grade powder (1, 30). Clinical use of the fluoroquinolones in cement products has not been reported, although limited in vitro data suggest that incorporation and elution occur (1). Although erythromycin (in combination with gentamicin) was applied in some of the earliest antibiotic-impregnated cement studies demonstrating clinical efficacy (7, 8), a subsequent study demonstrated inadequate elution of erythromycin from Palacos cement (46). Data for other macrolides and azalides are unavailable. Tetracycline and colistin fail to elute from Palacos cement in clinically meaningful quantities (46).

The elution characteristics of specific antibiotics vary depending on cement type, although Palacos cement provides more complete elution of most agents, including the commonly used aminoglycosides (30, 31). It is unclear whether antibiotic elution from commercially prepared beads can be consistently replicated by beads manufactured on site (33, 40).

Antibiotic release is biphasic, with the bulk occurring in the first hours to days postimplantation and the remaining elution persisting up to years (38, 43). In one study (2), gentamicin release from molded rods of PMMA occurred from the surface of the cement and through a network of voids and cracks in its matrix. In another study (3), it appeared to diffuse through the matrices of the cement. A significant proportion of antibiotic may be retained within the cement (2, 3, 21, 41). For example, in patients with total hip arthroplasties in which gentamicin cement was used, the total gentamicin content of wound drainage and urine excreted accounted for only approximately 25% of the gentamicin content of the cement (43).

While this discussion focuses on PMMA cement and beads, beads composed of alternative materials may prove more valuable in certain clinical settings. For example, plaster of Paris may be less suitable as a bone cement than PMMA, but antibiotic-impregnated beads composed of plaster of paris can provide for the more rapid release of high concentrations of antibiotics acutely when they are used for prophylaxis following an open fracture (6). Gentamicin-impregnated hydroxyapatite ceramic beads simulate a bone graft by serving as an osteoconductive matrix and, unlike PMMA beads, do not have to be removed when they are used to fill dead space (12). Gentamicin-impregnated polylactide-polyglycolide copolymer implants are biodegradable and, similarly, may not need to be removed (20).

TISSUE PENETRATION

The extent to which antibiotics diffuse from the high local concentrations impregnated in PMMA cement and beads into contiguous tissues has been analyzed in animal models and human studies. Concentrations in hematoma or seroma wound fluid, granulation tissue, and bone varied by the specific antibiotic tested, but they were prolonged, were higher than the observed concentrations in serum, and usually exceeded the MIC breakpoints used to define the in vitro susceptibilities of targeted pathogens (1, 14, 22, 38, 42, 45–48).

In a canine model with antibiotic (cefazolin, ciprofloxacin, clindamycin, ticarcillin, tobramycin, and vancomycin)-impregnated Simplex beads (0.1 to 0.3 g of antibiotic powder per g of cement powder) implanted into the tibia (1), antibiotic concentrations in seroma fluid near the implantation site were above the MIC breakpoints through at least the indicated sampling days for the following antibiotics: cefazolin, day 14; ciprofloxacin, day 3; clindamycin, day 28; ticarcillin, day 9; tobramycin, day 21; and vancomycin, day 3. With the exception of ticarcillin, antibiotic concentrations in the granulation tissue surrounding the beads exceeded 30 μg/ml 28 days after implantation. The concentrations in bone at 28 days were subinhibitory for ticarcillin, cefazolin, and tobramycin but were above the MIC breakpoints for ciprofloxacin, clindamycin, and vancomycin. The concentrations of cefazolin, ciprofloxacin, clindamycin, and vancomycin in serum were never detectable, while those of ticarcillin and tobramycin were subinhibitory for up to 6 h after implantation.

Considerable data from canine models demonstrate favorable pharmacokinetics for gentamicin-impregnated cement and beads (45–47). Gentamicin concentrations in hematomas after implantation of unformed cement in canine femurs were 7.7 to 24 μg/g (46), and after implantation of beads, the concentrations were approximately 100 to 200 μg/g for up to 2 weeks (47). The concentrations in connective tissue adjacent to the beads were 2.2 to 16 μg/g, and average concentrations in adjacent spongiosa and cortical bone were 6.7 and 2.8 μg/g, respectively, at 2 weeks (47). Even at 6 months after bead placement, when 70% of the initially incorporated gentamicin had been released from the beads, the concentrations in adjacent fibrous tissue and cancellous bone were 9.3 and 4.5 μg/g, respectively (45). Low concentrations were detectable in serum for 24 h, but gentamicin could be detected in urine for months (47).

Among patients who received total hip replacement with gentamicin-impregnated cement (46) and those treated for osteomyelitis with gentamicin-impregnated beads (45, 47), high drug concentrations, similar to those observed in canine

models, were achieved in wound secretions during the postoperative period. Tissue specimens obtained days to months after total hip arthroplasty with gentamicin cement demonstrated measurable gentamicin levels in connective tissue (4 to 36 μg/g), spongiosa (0.4 to 39 μg/g), and corticalis (0 to 3.4 μg/g) (46). Six months after placement, the average cortical gentamicin level for four patients was 1.4 μg/g, and drug was present in samples of connective tissue and bone from some patients 5 years after surgery (46). When gentamicin beads were removed from patients at 30 to 70 days postimplantation, cancellous bone sampled 5 to 10 mm from the beads had gentamicin concentrations of 1.6 to 4.3 μg/g, while the concentrations in cortical bone were 0 to 3.0 μg/g (45). Additional studies (38, 43, 48) have confirmed the high postoperative concentrations of gentamicin in fluids and tissues after insertion of cement or beads, low concentrations in serum (usually <2 μg/ml at 24 h), and prolonged concentrations in urine.

Information on tobramycin-impregnated cement and beads is more limited. Among patients receiving total hip arthroplasty revision with tobramycin-impregnated cement, postoperative concentrations in hematomas were approximately 20 μg/ml, concentrations in serum were <2 μg/ml, and concentrations in urine were approximately 14 μg/ml, gradually tapering down during the following 2 weeks (42). Among those with compound fractures treated prophylactically with tobramycin-impregnated beads, wound drainage and wound clot aspirates had drug concentrations averaging 19 and 9 μg/ml, respectively, on the first postoperative day, while the average concentration in serum was 0.4 μg/ml (14).

CLINICAL APPLICATIONS

Antibiotic-impregnated cement has been used prophylactically for total joint arthroplasties and as part of the treatment strategy when an infected arthroplasty is removed and replaced in a single step. Beads have been used when a delayed replacement is planned in infected arthroplasties, to treat chronic osteomyelitis, and, prophylactically, when repairing open fractures. Animal models have been used to define the efficacy of antibiotic-impregnated cement or beads in preventing and clearing bacteria from prostheses and bone. Clinical trials, even when they are controlled, prospective, and randomized, have often been flawed by low rates of accrual or retention.

Most animal and human studies have used gentamicin-impregnated beads and cement because of their stability, favorable pharmacokinetics, commercial availability in some countries, weak allergenicity, low systemic toxicity when applied locally, and favorable results when first used clinically; tobramycin has been substituted in the United States for the reasons enumerated above. The in vitro spectrum of the aminoglycosides, which includes activity against aerobic gram-negative bacilli and staphylococci, has also been deemed suitable, despite poor or no activity against streptococci, enterococci, and anaerobes (29, 36).

Prophylaxis for total joint arthroplasty. Animal studies have demonstrated the potential for antibiotic-impregnated cement to prevent bone and joint infections. When bacteria were inoculated into bone just prior to filling surgical defects with antibiotic-impregnated cement, infection was reduced. Gentamicin-impregnated cement prevented infections caused by *Staphylococcus aureus*, streptococci, and gram-negative organisms in rat tibias (15). Erythromycin- and colistin-impregnated cement prevented *S. aureus* and *Escherichia coli* infections in rabbit femurs (37). In a rabbit model of knee hemiarthroplasty, gentamicin-impregnated cement prevented infection when *E. coli* was inoculated into joints up to 7 days after surgery (41). Prevention of late infection after direct inoculation or hematogenous infection has not been demonstrated in animal models (5, 15, 41).

In Buchholz and Engelbrecht's (8) pioneering series of 1,115 total joint replacements with antibiotic cement, only one deep infection was reported in the first year. In a 1976 to 1978 Swedish prospective, randomized, multicenter controlled study comparing the efficacy of prophylactic penicillins or cephalosporins administered for 1 to 2 weeks with that of gentamicin-impregnated cement in 1,688 consecutive total hip arthroplasties, there were no differences in the rates of deep infection (1.6 versus 1.1%) or noninfectious prosthetic loosening (55 versus 50%) after 10 years of observation (26–28). No reports have compared the efficacy of systemic antibiotics plus antibiotic-impregnated cement with that of either treatment alone, and with the low infection rates already achieved with modern operative techniques, such a study would require a prohibitively large number of patients to demonstrate a statistically significant difference between these prophylaxis strategies (44).

Treatment of total joint arthroplasty infection. There are no animal data regarding the treatment of arthroplasty infections comparable to those obtained from studying prophylaxis, and limited available clinical data are relied upon to guide therapy. Most orthopedists believe that the optimal management of infected total arthroplasties requires removal of the infected prosthesis, careful debridement of infected devitalized tissue and old cement, and appropriate antibiotic therapy. Variables include the timing of reimplantation of the prosthetic joint (immediate versus delayed) and the specific combination of systemic and/or local antibiotics.

Some investigators favor immediate reimplantation to attempt to avoid second operations and hasten the overall recovery period (7, 10). Buchholz et al. (7) reported a 77% success rate with primary exchange operations with antibiotic-impregnated cement, usually without systemic antibiotics.

If delayed reimplantation is elected, beads can be used during the period between prosthesis removal and reimplantation. In a comparative trial of 28 patients with infected total hip or knee arthroplasties, the efficacy of 6 weeks of intravenous antibiotics was compared with that of gentamicin beads prior to delayed reconstruction (32). Although recurrent infection was more common among those treated with systemic antibiotics, it seemed to be related more to patient variables than to the antimicrobial regimen. No study has compared the efficacy of systemic antibiotics plus antibiotic beads with that of either therapy alone.

Treatment of chronic osteomyelitis. Although gentamicin-impregnated cement prevented the development of *S. aureus* osteomyelitis in canine tibias, it could not clear established infections (18). Gentamicin-impregnated beads were more effective, however, in another model of established osteomyelitis in canine femurs (45). In rabbits, osteomyelitis of the radius was produced by inoculating a devascularized bone segment with *S. aureus*. After treatment with debridement alone or in conjunction with antibiotic-free beads, gentamicin-impregnated beads, intravenous ceftriaxone, or ceftriaxone plus gentamicin-impregnated beads, cure rates were 43, 27, 79, 92, and 100%, respectively (16). When dead iliac crest bone which had been preincubated with *S. aureus* was implanted into muscle wounds of rabbits, tobramycin-impregnated beads plus systemic gentamicin or cefazolin reduced the bacterial load more than systemic antibiotics alone, but the infection was not eradicated (11). This demonstrated the primacy of thorough debridement in the management of osteomyelitis, even when antibiotic-impregnated beads are used.

Few controlled clinical trials have been performed to assess

the efficacy of beads in the treatment of osteomyelitis. Fifty-two patients with infected nonunions receiving debridement and reconstructive surgery were randomized to receive either gentamicin-impregnated beads with perioperative (2 to 5 days) parenteral antibiotics or 4 weeks of parenteral antibiotics, with success rates of 89 and 83%, respectively (9). In the one large, prospective, multicenter study (4) in which 384 patients with established chronic osteomyelitis were similarly randomized, there was nonsanctioned crossover by 145 of 194 patients in the bead group to the parenteral antibiotic group, making comparison of the two treatment strategies impossible. The investigators' final analysis emphasized debridement, soft tissue covering, and individual patient factors as important variables in this complex infection.

Prophylaxis for open fracture repair. During the acute management of severe open fractures it is not possible to define the full extent of devitalized tissue which will eventually require debridement. In this setting, the introduction of local antibiotics in a vehicle to fill the dead space may theoretically reduce bacterial contamination adequately to avert subsequent infection. Data from animal models of the prevention of osteomyelitis (11, 18, 45) could be used to infer a possible role for beads in this setting, and the limited clinical data support this assumption. In a review of 1,085 consecutive cases of compound limb fractures (35), all of which were debrided and stabilized, 845 were treated with gentamicin-impregnated beads plus systemic antibiotic prophylaxis and 240 received systemic antibiotics alone (based upon the surgeon's preference). The overall infection rate was significantly lower in the group receiving beads (3.7 versus 12%), and the differences were greatest among patients with severe soft tissue damage, gross contamination, or impaired vascularity. Few data were presented regarding possible selection bias or confounding variables in the two study groups, such as culture results, wound management, or comorbid conditions. It would be desirable to evaluate the efficacy of beads in the prophylaxis of open fractures prospectively.

SAFETY ISSUES AND UNRESOLVED QUESTIONS

Serious adverse reactions, including allergic reactions, due to antibiotic-impregnated cement or beads have not been reported, and adverse reaction rates were lower than those among patients receiving systemic antimicrobial agents (4). Among 14 patients treated with gentamicin-impregnated beads, with or without systemic antibiotics, one experienced reduced hearing at a single frequency by audiometry (23), and measurements of tubular and glomerular function in five patients showed no abnormalities (49).

Although the effect of antibiotics on the mechanical properties of bone cement varies depending on the quantity and type of antibiotic, it is minor by most criteria (31), but long-term follow-up may be necessary to uncover an effect on rates of mechanical failure.

Theoretical problems with prolonged implantation of antibiotic-impregnated beads include secondary infection in the presence of a foreign body and the emergence of bacterial resistance. These issues have not been well studied but do not seem to be major clinical problems. After removal of gentamicin-impregnated beads placed to treat infected nonunions in 23 patients, 20 were culture positive. However, patients received perioperative parenteral antibiotic for 2 to 5 days after bead removal, and the presence of bacteria around the beads had no effect on the ultimate result of arrested infection or healed nonunion (9). Among 52 patients with chronic osteomyelitis treated with gentamicin-impregnated beads, 5 of 35 who had elective bead removal had recurrent infection, whereas none of 17 patients whose beads were left in place for approximately 3 years had recurrent infection. The investigators concluded that the high initial antibiotic concentrations at the wound site were sufficient to overcome resistance (as defined by MIC breakpoints based on lower achievable concentrations in serum) and that bacteria were suppressed until the regenerating bony environment eradicated residual organisms (24).

While the emergence of bacterial resistance in individual patients treated with antibiotic-impregnated cement and beads has not been perceived as a problem, there has been a change in the susceptibilities of staphylococci, the most common bacteria causing bone infections. At our medical center, methicillin-resistant staphylococci are now quite common (*S. aureus*, ≈30%; *Staphylococcus epidermidis*, ≈75%; and *Staphylococcus haemolyticus*, ≈90%), and aminoglycoside resistance among methicillin-resistant strains of the three species is ≈25, 60, and 80%, respectively. The selection of antibiotics to be used in cement products may need to be reconsidered in light of changing bacterial resistance patterns.

CONCLUSIONS

The theoretical advantages of antibiotic-impregnated cement and beads in the treatment and prophylaxis of orthopedic infections are supported by the results of some animal and human studies. Evidence of their efficacy, particularly in comparison with those of systemic antibiotics or with those of antibiotic-impregnated cement or beads in combination with systemic antibiotics, has not been firmly established. Fortunately, adverse reaction rates seem to be low.

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